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सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***673/Del/02*** *dated* ***24th June 2002.***

Witness my hand this 08th Day of September 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

0673-2

FORM 1

24 JUN 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" A PROCESS FOR THE PREPARATION OF ROBUST FORMULATION OF VALACYCLOVIR HYDROCHLORIDE TABLETS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ASHISH GOGIA
b. ROMI BARAT SINGH
c. PANANCHUKUNNATH MANOJ KUMAR
d. SUNILENDU BHUSHAN ROY
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001–10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, ASHISH GOGIA, ROMI BARAT SINGH, PANANCHUKUNNATH MANOJ KUMAR, SUNILENDU BHUSHAN ROY, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Ashish Gogia

(ASHISH GOGIA)

b. Romi Singh

(ROMI BARAT SINGH)

c.

(PANANCHUKUNNATH MANOJ KUMAR)

d.

(SUNILENDU BHUSHAN ROY)

e.

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3.
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **681626** dated : **02.05.2002** drawn on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **21ST** day of **June, 2002.**

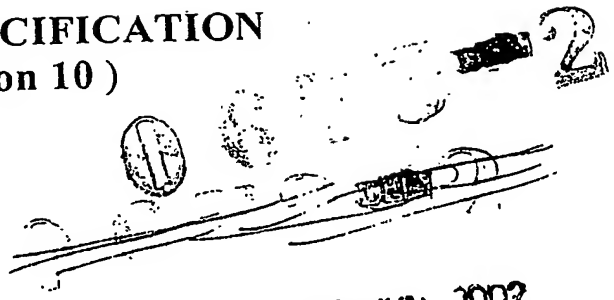
For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)



24 JUN 2002

A PROCESS FOR THE PREPARATION OF A ROBUST FORMULATION OF VALACYCLOVIR HYDROCHLORIDE TABLETS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a new robust formulation of valacyclovir hydrochloride tablets.

Valacyclovir is the L-valine ester of acyclovir and it has been shown to posses improved bioavailability while retaining the anti-viral properties of acyclovir. The hydrochloride salt is the preferred form of this compound. Valacyclovir and its salt including the hydrochloride salt were first disclosed in the US Patent No. 4,957,924 by Glaxo Wellcome Inc.

In a subsequent patent US 6,107,302, Glaxo Wellcome have disclosed that valacyclovir hydrochloride can exist in various forms, particular among them is valacyclovir hydrochloride which is anhydrous and crystalline and which surprisingly has good pharmaceutical properties. This anhydrous form has a water of hydration content of not more than 3% by weight. This anhydrous crystalline valacyclovir HCl has been shown to be chemically and physically stable with good formulation and storage properties.

In their US Patent No. 5,879,706, Glaxo Wellcome Inc have disclosed that during the development of a tablet formulation containing a high proportion of the drug, they often encountered difficulty in obtaining tablets of sufficient hardness and friability for pharmaceutical handling and for film coating. As per the US Pharmacopoeial requirements, tablets should have a friability not exceeding 1%. If the tablets are too friable, they will chip or break during coating, packaging and transport.

In an effort to increase the hardness of the tablets and improve their friability, the inventors tried several remedies such as increasing the compression force, decreasing lubricant, increasing binder concentration etc, without any success.

Finally, they found a unique tablet formulation containing 0.05% to 3% w/w colloidal silicon dioxide and extragranular microcrystalline cellulose as the filler which was robust and had substantially improved friability and hardness. Colloidal silicon dioxide and extragranular microcrystalline cellulose appear to have synergistic effect and robust tablets of valacyclovir can consistently be made to an acceptable hardness without introducing stress cracks even under a high compression force. This formulation also had satisfactory disintegration time and lubrication properties. Anhydrous crystalline form of valacyclovir hydrochloride having no more than 3% water of hydration was used as the active ingredient in accordance with this invention.

We have surprisingly found that it is possible to prepare a robust tablet of valacyclovir which exhibits acceptable hardness and has low friability even without the presence of the combination of colloidal silicon dioxide and extragranular microcrystalline cellulose.

We have found that when the active used in the formulation is valacyclovir hydrochloride having a water of hydration of more than 3% and a particle size of 100% less than 355 μm, instead of anhydrous crystalline valacyclovir hydrochloride disclosed in the prior art, it exhibits improved pharmaceutical handling characteristics and results in a more robust formulation. Preferably, valacyclovir hydrochloride has a water of hydration of more than 4% w/w.

It is an object of the present invention to provide a stable and robust tablet formulation comprising valacyclovir hydrochloide having a water hydration more than 3% and a particle size of less than 355 μm.

Valacyclovir is a high dose drug and the tablet typically comprises at least 50% of the drug. The drug characteristics therefore play an important role in determining the characteristics of the final formulation. When we formulated tablets comprising anhydrous crystalline valacyclovir hydrochloride, we faced problems similar to those described in US 5,879,706. However, when the water of hydration in valacyclovir hydrochloride was increased to more than 3% and the drug particle size kept at less than 355μm, we surprisingly found that the problems of friability, low hardness, sticking to the tablet dies etc disappeared. The hydrated form of valacyclovir hydrochloride was surprisingly easier to formulate, and the formulation thus made was not dependent upon the presence of silicon dioxide and extragranular microcrystalline cellulose for its low friability and excellent hardness. Without intending to be limited by theory, we feel that the increased robustness of the tablets containing high amounts of the hydrated drug may be because the water of hydration helps in the binding of the drug and excipients resulting in a granulate that has better compressibility characteristics.

The particle size of the drug also played a critical role in determining the compressibility, hardness and friability of the tablet formulation. The particle size of the drug was maintained at 100% below 355μm, preferably it was 100% below 250μm.

The tablet formulation in accordance with the present invention further contains other pharmaceutically acceptable excipients such as those belonging to the category of fillers, binders, lubricants and the like.

According to the preferred aspect of the invention there is provided a tablet comprising at least 50% w/w valaciclovir hydrochloride having a water of hydration of more than 3%, a binding agent,

disintegrant, and a lubricant wherein valaciclovir hydrochloride is present within the granules of the tablet and wherein the friability of the tablet does not exceed 1%, and the hardness is at least 10 KP.

The binding agent used in accordance with this invention is selected from those commonly known in the art. The binder is preferably selected from amongst cellulose ethers, such as hydroxypropyl methylcellulose and hydroxypropyl cellulose, and polyvinyl pyrrolidone sold under the trade name povidone which is available as K30 and more preferably K90.

The binding agent is preferably present from about 0.5% to about 5% w/w of formulation. We have observed that the use of a cellulose ethers as extragranular dry binders increase the hardness and improves the friability of the formulation. The extragranular dry binders are present from about 1-5% w/w of the formulation, preferably they are present at 1-2% w/w of the formulation. The drug and excipients may be granulated following either the wet or the dry granulation process.

Wet granulation was the process of choice for granulation. The fluid uptake during granulation played a critical role in determining the hardness, friability and the disintegration time of the tablets. The fluid uptake by the dry blend was preferably more than 10% during granulation. Fluid uptake less than 10% resulted in highly friable tablets. The maximum fluid uptake was preferably less than 16% as more than that resulted in wet massing. The fluid uptake during granulation and the moisture content in the final granules played a critical role in determining the hardness and friability of the resulting tablets.

The formulation in accordance with the present invention may further contain disintegrants selected from those commonly known in the art. They include clays such as bentonite, kaolin or veegum, celluloses such as microcrystalline cellulose or croscarmellose sodium and non-ionic disintegrants such as cross-linked polyvinyl pyrrolidone sold under the trade name of cross povidone. The disintegrants may be present at about 0.5% to about 7% w/w of the formulation.

The granules thus prepared were dried and the effect of the moisture content in the granules in the tablet formulation was monitored. It was observed that granules containing more than 4% moisture content resulted in robust tablets.

The formulation may also contains fillers such as those selected from amongst lactose, microcrystalline cellulose and the like.

The lubricants are present in an amount of about 0.1% to about 2.0% w/w preferably about 0.1% to about 1.5%. They may suitably be selected from those commonly known in the art such as colloidal silicon dioxide, magnesium stearate, talc and the like.

The following examples further exemplify the invention and are not intended to limit the scope of the invention.

TABLE -1

EXAMPLES 1 - 3

EFFECT OF EXTRAGRANULAR BINDERS ON THE HARDNESS AND FRIABILITY OF TABLETS.

Ingredients	#1	#2	#3
INTRAGRANULAR			
Valacyclovir hydrochloride	584.03	584.03	584.03
Microcrystalline cellulose	87.97	80.97	60.97
Crospovidone	14	14	14
Povidone K30	7	7	7
Purified water	q.s.	q.s.	q.s.
EXTRAGRANULAR			
Microcrystalline cellulose	-	-	5
HPMC E5 Premium	-	7	-
HPC-L	-	-	14
Magnesium stearate	7	7	7
TABLET WT.	700	700	700
HARDNESS	15-18KP	20-28KP	25-38KP
FRIABILITY	>1%	>0.2%	0.01%
Disintegration Time (Minutes)	20	20	22
STICKINK/PICKING	Slight sticking	negligible	NIL

DIFFICULT HANDLING AND SUBSEQUENT FILM COATING

Valacyclovir hydrochloride having a particle size of less than 250μm and a degree of hydration between 5-7% was used in all the three formulations. The tablets containing no extragranular binder (Example 1) had unacceptable friability which resulted on difficulty in handling and subsequent film coating. Tablets prepared in accordance with Example 2 were used for all subsequent studies. Tablets containing even 1-2% of a cellulosic binder (Examples 2 and 3) showed low friability and acceptable hardness, and improved compressibility and dissolution characteristics

TABLE - 2

EFFECT OF PARTICLE SIZE DISTRIBUTION OF VALACYCLOVIR HYDROCHLORIDE

Ingredients	#1	#2	#3	#4
% RETAINED ON #22 (710 μm)	4.2 %	NIL	NIL	NIL
% RETAINED ON #44 (355 μm)	14.2%	18.6%	NIL	NIL
% RETAINED ON #60 (250 μm)	24.7%	25.7%	23.7%	NIL
Hardness(Kp)	10kP	12kP	15kP	28kP
Friability(%release)	>2%	>2%	>1%	.008%
Disintegration Time (minutes)	<6	6-8	10-12	15-20
Coating	Tablets could not be coated	Tablets could not be coated	Tablets when coated showed tendency to crack and edge chipping and erosion.	Tablets were coated under normal coating parameters

Tablets were formulated as given in Example 2 of Table 1 using drug containing a particle size of less than 355 μm, or more preferably less than 250μm had excellent hardness and low friability (Example 4 above). When the drug particles used in the composition had more than 20% of the particles more than 250um and the rest below it, the granules of that batch were difficult to compress, had low hardness and the friability was more than 1%.

TABLE - 3

EFFECT OF FLUID UPTAKE

Ingredients	#1	#2	#3	#4
Fluid uptake	8%	12%	14%	16%
Core tablets parameters	Tablets showed capping at hardness above 25 kP	Tablets took hardness upto 35kP	Tablets took hardness upto 48kP	Tablets took high hardness, but processing required wet massing
Friability	>2%	<1%	0.002%	0.002%
Disintegration Time (minutes)	12-14	15-20	15-20	15-20
Processing	Tablets were difficult to coat	Tablets took hardness up to 35kP and 48kP with ease of compressibility. There was no sticking or picking encountered. Friability improved with fluid uptake. The tablets showed no capping /lamination/cracking/ chipping during coating or stress testing.		Wet massing is difficult. Since granules are hard, the formulation becomes dependent on % of fines and particle size distribution of the blend for compression.

As can be seen above the fluid taken up by the dry blend during granulation played a critical role in determining the hardness and friability of the resulting tablets. Fluid uptake of between 10-16% was most suited for valacyclovir tablets. After granulation tablets were formulated as given in Example 2 of Table 1.

TABLE - 4

EFFECT OF WATER CONTENT IN THE DRIED GRANULES PRIOR TO ADDITION OF EXTRAGRANULAR EXCIPIENTS

Ingredients	#1	#2	#3	#4
Water content	2.8%	5.4%	8.9%	12.3%
Friability	>1%	0.45%	0.005%	0.002%
Hardness(range)	20-25kP	25-30kP	25-35kP	25-35kP
Disintegrant Time (minutes)	12-15	15-20	16-20	16-20
Processing	Tablets had to be coated with pan rotating at min speed and high spray rate to prevent edge chipping.	Tablets were coated under normal coating parameters with no issues of cracking/ chipping		

The water content in the dried granules prior to their being mixed with the extragranular excipients and tabletted was measured for its effect on the hardness and friability. As can be seen from the data above granules having a water content of more than 5.0% when formulated as tablets had good hardness and low friability.

WE CLAIM :

1. A process for the preparation of a stable and robust pharmaceutical tablet composition comprising granulating valacyclovir hydrochloride having a water of hydration of more than 3% and a particle size less than 355μm together with other pharmaceutically acceptable excipients and compressing the resulting granules to tablets, wherein the tablet has a hardness of at least 10 KP and friability of less than 1%.

2. A process for the preparation of pharmaceutical composition as described in claim 1 wherein valacyclovir hydrochloride preferably has a water of hydration of more than 4%.

3. A process for the preparation of pharmaceutical composition as described in claim 1 wherein valacyclovir hydrochloride preferably has a particle size of less than 250μm.

4. A process for the preparation of pharmaceutical composition as described in claim 1 wherein the formulation contains other pharmaceutically acceptable excipients such as fillers, binders, disintegrants and lubricants.

5. A process for the preparation of pharmaceutical composition as described in claim 4 wherein the fillers are selected from amongst lactose and microcrystalline cellulose.

6. A process for the preparation of pharmaceutical composition as described in claim 5 wherein the fillers is present from about 5% to about 40% w/w of the formulation.

7. A process for the preparation of pharmaceutical composition as described in claim 4, wherein the binder is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone and the like.

8. A process for the preparation of a pharmaceutical composition as described in claim 7 wherein the binder is present at 0.05% to 5% w/w of the formulation.

9. A process for the preparation of pharmaceutical composition as described in claim 7 wherein a portion of the binder is present extragranularly as dry binder.

10. A process for the preparation of pharmaceutical composition as described in claim 9 wherein the extragranular dry binder is present at concentration of between 0.05% - 2% w/w of the formulation.

11. A process for the preparation of pharmaceutical composition as described in claim 4 wherein the disintegrant is selected from amongst clays such as kaolin, bentonite or veegum, celluloses such as microcrystalline cellulose or croscarmellose sodium and non-ionic disintegrants such as polyvinylpyrrolidone.

12. A process for the preparation of a pharmaceutical composition of claim 11 wherein the disintegrant is present from about 0.5% to about 7% w/w of the formulation.

13. A process for the preparation of a pharmaceutical composition wherein the valacyclovir hydrochloride having a water of hydration of more than 4% a drug particle size of less than 355μm is mixed with other pharmaceutically acceptable excipients and wet granulated wherein the fluid uptake during granulation was between 8-16%.

14. A process as described in claim 13 wherein the fluid uptake is between 12-16%.

15. A process as described in claim 13 wherein the dried granules have a water content of more than 4.0% w/w.

16. A process as described in claim 1 wherein the pharmaceutical composition is a tablet.

17. A process as described and exemplified herein.

Dated this **21ST** day of **June, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary